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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,101	08/27/2001	Mary E. Gerritsen	GENENT.072A2	4279

25213 7590 09/13/2005

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EXAMINER	
BELYAVSKYI, MICHAIL A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/940,101	GERRITSEN ET AL.	
	Examiner	Art Unit	
	Michail A. Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,27 and 85-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,27 and 85-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 07/28/05 is acknowledged.

Claims 26, 27 and 85-93 are pending.

Claims 26, 27 and 85-93 , as they read on the methods for inhibiting proliferation or migration of smooth muscle cells comprising treating said smooth muscle cells with an effective amount of an antagonist antibody of a native ErbB4 receptor of SEQ ID NO:2, are under consideration in the instant application.

In view of the amendment, filed 07/28/05 the following rejections remain:

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 26, 27 and 85-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* method for reducing proliferation or migration of vascular smooth muscle cells in cell culture, comprising administering an effective amount of antibody to native ErbB4 receptor does not reasonably provide enablement for a method for reducing proliferation or migration of smooth muscle cells *in vivo*, comprising administering an effective amount of antibody to native Erbb4 receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Actions , mailed on 03/01/05.

Applicant's arguments, filed 07/28/05 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) the specification and claims as originally filed provided adequate support for in vivo method claims . Applicant further asserts that the support for *in vivo* enabling is provided on pages 55-62 of the current Specification and provided examples regarding the claimed therapeutic composition, including explicit dosage range; (ii) one of ordinary skill in the art would understand and accept that *in vitro* data of the specification that an effective amount of antibody to native Erbb4 receptor will reduce smooth muscle cell proliferation and that such treatment would be effective in vivo; (iii) the provided references of Hoe et al., Hayashi et al., and Mizutani et al., all teach that *in vitro* assays of smooth muscle cell proliferation and migration were well known at the time the application was filed and were accepted as relevant to clinical questions.

With regards to the statement that "the support for *in vivo* enabling is provided on pages 55-62 of the current Specification and provided examples regarding the claimed therapeutic composition, including explicit dosage range ". It is noted that the examples disclosed on pages 55-62 in the instant Specification are prophetic examples that indicate what the inventor thinks might happen in the experiments which have not actually been performed.

With regards to the statement that " one of ordinary skill in the art would understand and accept that *in vitro* data of the specification that an effective amount of antibody to native Erbb4 receptor will reduce smooth muscle cell proliferation and that such treatment would be effective in vivo". The issue raised by the Examiner was not about the ability one skill in the art to understand and accept *in vitro* data. Moreover, the Examiner acknowledge that specification, being enabling for *in vitro* method for reducing proliferation or migration of vascular smooth muscle cells in cell culture. However, as has been stated in the previous Office Action since no animals were used as model system to reduce proliferation or migration of vascular smooth muscle cells *in vivo*, it is not clear that reliance on the *in vitro* data that culturing human aortic smooth muscle cells in the presence of effective amount of antibody to native Erbb4 receptor will reduce cell proliferation as was monitor by decreasing in the uptake of BrdU into said cell (Example 2) and reduce migration of said cells (Example 3) accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively reduce proliferation or migration of vascular smooth muscle cell *in vivo* by administrating effective amount of antibody to native ErbB4 receptor. The specification does not teach how to extrapolate data obtained from an *in vitro* assay studies to the development of effective in vivo mammalian therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the therapeutic package exemplified in the specification. In addition, Topol et al. (JAMA 278: 479-484, 1997) states that a large number of pharmacological agents have failed to reduce stenosis or restenosis or improve long-term clinical outcomes and that only the large-scale trial that reported an effect was using abciximab (see page 479, right hand column). An effective protocol for reducing proliferation or migration of smooth muscle cells *in vivo* comprising administering an effective amount of antibody to native ErbB4 receptor of SEQ ID NO:2 in the absence of *in vivo* clinical data are unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the antibody may not reach the target area because, i.e. the antibody may not be able to cross the mucosa or the antibody may be adsorbed by fluids, cells and tissues where the antibody has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

With regards to applicant's comments that "the provided references of Hoe et al., Hayashi et al., and Mizutani et al., all teach that *in vitro* assays of smooth muscle cell proliferation and migration were well known at the time the application was filed and were accepted as relevant to clinical questions". The examiner disagrees with Applicant's interpretation of the prior art.

Clearly, *in vitro* assays of smooth muscle cell proliferation and migration were well known at the time the application was filed. However, Applicant's attention is drawn to page 475 of Hou et al., reference. It is explicitly stated that " **these in vitro results should be interpreted with some caution**, because a previous report has suggested that SMCs in vivo in the rat carotid do not express the $\alpha 2\beta 1$ integrin receptor. Further work is necessary to determine whether this holds true for all species and tissues. Similarly, Hayashi et al., explicitly indicates that his studies were based on recent clinical studies that have demonstrated the clinical usefulness of cilostazol as cAMP analogue to treat human restenosis" (see page 237 in particular). In other words, even the additional references cited by Applicant supports the examiner position that since no animals were used as model system to reduce proliferation or migration of vascular smooth muscle cells *in vivo* , it is not clear that the skilled artisan could predict the efficacy and therapeutic outcome of the claimed method of inhibiting proliferation or migration of smooth muscle cells *in vivo*, comprising administering an effective amount of antibody to native Erbb4 receptor of SEQ ID NO:2.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of inhibiting proliferation or migration of smooth muscle cells *in vivo*, comprising administering an effective amount of antibody to native Erbb4 receptor of SEQ ID NO:2 in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 26 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Paten 5,811,098 in view of Krymskaya et al (Am. J. Physiol.1999, 276, pages L246-L255) or WO 99/02681 for the same reasons set forth in the previous Office Action, mailed 03/01/05.

Applicant's arguments, filed 07/28/05 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) the is no motivation in the references or in the art to combine the references, nor do the cited references provide a reasonable expectation of success; (ii) US Patent '098 does not disclosed nor suggest a method for controlling excessive proliferation or migration of smooth muscle cell (ii) Krymskaya et al., does not reveal that ErbB4 receptors play a role in smooth muscle proliferation, thus provides no teaching that one could control or inhibit smooth muscle proliferation ; (iii) WO 99/02681 nowhere suggests or provide motivation that antagonists to ErbB4 receptor might be useful to control smooth muscle proliferation; (iv) Applicant's hybridomas and the antibodies they produce are uniquely and partentably distinct from the anti Erb4 antibody of US Patent' 098.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

It is also noted that the amended claims are drawn to a method for **reducing proliferation** or migration of smooth muscle cells not to a method **for controlling excessive proliferation** or migration of smooth muscle cell as asserted by Applicant.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the teachings of US Patent '098 pertaining to the a method of controlling excessive proliferation of cancer cells by administering an neutralizing antibodies to native HER4 receptor and the fact that said HER4 receptor (SEQ ID NO: 2) that is 100% identical to SEQ ID NO:2 of ErbB4 receptor of the

current application and the teachings of Krymskaya et al., and WO '681 indicating that HER4 receptor play a pivotal role in regulation of proliferation of smooth muscle cells would have led one of ordinary skill in the art at the time the invention was made to combine the references to obtained a method controlling excessive proliferation or migration of smooth muscle cells *in vitro* comprising administering an effective amount of an antibody of a native ErbB4 receptor of SEQ ID NO:2.

Moreover, one skill in the art would be expected to recognized the same receptor that play a pivotal role in regulation of proliferation of smooth muscle cells, i.e. HER4 receptor will also play an important role in regulation of proliferation of vascular smooth muscle cells since said cells are an obvious variation of smooth muscle cells. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

US Patent '098 teaches a method of controlling excessive proliferation of cancer cells by administering an antibodies to native HER4 receptor (see entire document, Abstract in particular). US Patent '098 further teach that antibodies is a neutralizing antibody, chimeric, humanized or human antibody or glycosylated antibody (see columns 18-19 in particular). US Patent '098 also teach that said antibodies can be used to block signal transduction mediated through HER4 receptor, thereby inhibiting undesirable cell function and behaviors, including proliferation and migration (see column 22, lines 44-66 in particular). US Patent '098 teach that said antibody can be used *in vitro* for various diagnostics and treatment purposes (see columns 21, 23 and 54 in paricular). US Patent '098 teaches an amino-acid sequence of HER4 receptor (SEQ ID NO: 2) that is 100% identical to SEQ ID NO:2 of ErbB4 receptor of the current application (see attached sequence alignment).

US Patent '098 does not teaches a method of controlling excessive proliferation or migration of smooth muscle cells *in vitro*.

Krymskaya et al. teach the presence of ErbB4 receptor on the human airway smooth muscle cells (see entire document, abstract in particular). Krymskaya et al. teach that this receptor play a pivotal role in regulation of proliferation of smooth muscle cells and that uncontrolled proliferation of smooth muscle cells results in various pathologies and that regulation of proliferation of said cells has potential significance in treating said pathologies. Applicants attention is respectfully directed to abstract and page L254.

Similarly , WO 99/02681 teaches the presence of ErbB4 receptor on smooth muscle cells and that blocking signal transduction pathway mediated through this receptor can effect mitotic

activity of cells expressing said receptors (see entire document, page 8, lines 35 – 40 and page 17, lines 27-35 in particular).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Krymskaya et al ., or WO 99/02681 to those of US Patent '098 to obtain a claimed method for controlling excessive proliferation or migration of smooth muscle cells in vitro comprising treating said cells with antibody to ErbB4 receptor of SEQ ID NO:2.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because signal transduction mediated through ErbB4 receptor plays a pivotal role in regulation of proliferation of smooth muscle cells and uncontrolled proliferation of smooth muscle cells results in various pathologies and regulation of proliferation of said cells has potential significance in treating said pathologies as taught by combined teaching of Krymskaya et al. and WO 99/02681 . Moreover, one skill in the art would be expected to recognized the same receptor that play a pivotal role in regulation of proliferation of smooth muscle cells, i.e. HER4 receptor will also play an important role in regulation of proliferation of vascular smooth muscle cells since said cells are an obvious variation of smooth muscle cells. This uncontrolled proliferation can be blocked by a method taught by US Patent '098 using antibodies to ErbB4 receptor, that will block signal transduction mediated through ErbB4 receptor .

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

With regards to Applican's comments that "Applicant's hybridomas and the antibodies they produce are uniquely and partentably distinct from the anti Erb4 antibody of US Patent' 098".

It is noted that only claim 26 is rejected under 35 U.S.C. 103(a). Claim 26 does not recites using antibodies produced by Applicant's hybridomas. However, it is the examiner position that an antibody to native HER4 receptor taught by US Patent '098 would obviously bind to the same epitope as an antibody recited in the instant claim 26, because an amino-acid sequence of HER4 receptor taught by US Patent '098 is 100% identical to SEQ ID NO:2 of ErbB4 receptor of the current application. Since the office does not have a laboratory to test the reference antibody, it is applicant's burden to show that the reference antibody would not competes for binding with antibodies produced by Applicant's hybridomas.

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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